A 12

synthesized and have been shown to confer protection against attack by pathogenic organisms or their products *in vitro* and *in vivo*.

REMARKS

With this amendment, Claims 1-9, 15, 25, 36-37, 41, 43, 45-70, 73-85, 88-91, 94, 97-107, and 110 are pending examination. New claims 117-119 are added. Claims 10-14, 16-24, 26-35, 38-40, 42, 44, 71, 86, 87, 92, 93, 95, 96, 108, 109, and 111-116 are withdrawn from consideration as being drawn to nonelected inventions. For convenience, the Examiner's rejections are addressed in the order presented in the July 3, 2002 Office Action. Appendix A provides the version with markings to show changes made to the abstract. Appendix B provides the version with markings to show changes made to the claims. Also for the Examiner's convenience, Appendix C is included listing all pending and amended claims.

I. Status of the Claims

Claim 36 is amended to add the word "and" before the last species of the Markush group. This amendment adds no new matter. Claims 52, 53, and 60 have been amended to read "a mimic of a receptor for a toxin or adhesion of a pathogenic organism." Claim 52 is also amended to read glycosyltransferases, rather than transferases. These amendments add no new matter.

Claims 62 and 101 are amended to read the gut of the animal or the mammal, respectively. Similarly, claim 79 has been amended to read the gastrointestinal mucosal surface, rather than the gut. These amendments add no new matter.

Claims 63, 80, and 102 are amended to read a colicin from the major families of colicins, rather than the major families of colicins. These amendments add no new matter. Claims 64, 65, and 75 are amended to read "at least one" rather than "all or some of the." These amendments add no new matter.

Claims 67 and 110 have been amended to read comprising rather than including. These amendments add no new matter. Claims 73, 74, and 97 are amended to

recite said delivery microorganism, rather than said organism. These amendments add no new matter.

Claims 84 and 106 are amended to read the microorganism is killed before administration of the pharmaceutical preparation or before administration to the mammal, respectively. Support for these amendments is found in the specification at, for example page 22, lines 17-24. These amendments add no new matter.

Claims 89-90, 97-107, and 110 are amended to recite "the receptor" rather than "a receptor." These amendment adds no new matter.

Claims 58, 61, 66, 74, 75, 83, 97, and 107 are amended to correct obvious typographical errors. These amendments add no new matter.

New claims 117-119, directed to recombinant E. coli are added. Support for claim 117 is found throughout the specification, and at original claims 1 and 58. Support for claim 118 is found, for example, at Examples 1 and 2, pages 37-54, and at original claim 38. Support for claim 119 is found, for example, at Example 3, pages 54-59, and original claim 39. These amendments add no new matter.

II. Priority

Applicant's continue to assert that the priority for the application is based on an Australian application filed in that country on September 10, 1999. Applicants include a certified copy of the priority document from the Australian Patent Office for filing with the USPTO.

III. Information Disclosure Statement

At the request of the Examiner, Applicants provide a supplemental IDS listing U.S. patent documents and copies of those documents. The submission of the U.S. patent documents is not an admission and Applicants respectfully request the Examiner to consider the documents.

IV. Specification

The Examiner objected to the use of the word means in the abstract of the application. Applicants have amended the abstract to remove the word means and to correct other typographical errors. Applicants believe the abstract is now in compliance with the requirements for proper language and format and respectfully request the Examiner to withdraw the objection.

V. Claim Objections

The Examiner objected to claims 58, 61, 65-67, 74-75, 83, 98, 105, 107, and 110 because of informalities, including typographical errors. Applicants have made the following corrections to the claims. Commas have been inserted in claims 58, 61, 83, and 105. A comma has been removed from claim 107. Misspellings have been corrected in claims 65, 66, and 74. In claims 67 and 110, the word comprising has been substituted for the word including. A grammatically incorrect phrase has been corrected in claim 75.

VI. The Claimed Invention

The claimed invention encompasses novel recombinant microorganisms that express extracellular sugar or oligosaccharide moieties to mimic receptors of toxins or adhesins from pathogenic organisms. The recombinant organism expresses at least one exogenous glycosyltransferase to facilitate synthesis of the receptor mimic. The claimed recombinant organisms block binding of toxins or adhesions to oligosaccharide-based receptors found on mammalian cells. Thus, the claimed invention is useful to treat subjects infected by pathogenic organisms. Claims are also directed to pharmaceutical preparations comprising the claimed recombinant microorganisms and to methods of administering the claimed recombinant microorganisms.

Previously, attempts had been made to use purified, chemically-synthesized oligosaccharides to block binding of pathogenic organisms to oligosaccharide-based receptors. However, chemical synthesis of oligosaccharides is expensive and the correct conformation of the oligosaccharide is difficult to obtain by

such methods. Applicants were the first to recognize that intact microorganisms can be used to inexpensively produce the oligosaccharide receptor mimics in the correct extracellular conformation, for delivery of the receptor mimic to a subject infected with a pathogenic organism.

VII. Claim Rejections Under 35 U.S.C. §112, First Paragraph, Written Description

Claims 1-9, 15, 25, 36-37, 41, 43, 45-70, 73-85, 88-91, 94, 97-107, and 110 were rejected as allegedly containing subject matter that was not described in the specification as originally filed. In the Office Action, the Examiner observes that the purpose of the written description requirement is to convey to one of skill in the art that the inventor was in possession of the invention as of the filing date. The Examiner also alleges that the genus of recombinant microorganism is not claimed in a specific biochemical or molecular structure to be envisioned by one of skill in the art.

Applicants respectfully traverse this rejection on three grounds. First, in requiring specific biochemical or molecular structures for each embodiment, the Office Action applied an improper standard for adequacy of written description. Second, the Office Action improperly rejected original claims as lacking adequate written description. Third, the Office Action improperly required reduction to practice of all embodiments to demonstrate possession of the claimed invention.

With regard to the structure of the claimed invention, the Examiner is apparently referring to *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997). "A description of a genus. . . may be achieved by means of . . . a recitation of structural features common to the members of the genus . . . ." *Lilly*, 43 USPQ2d at 1406.

Applicants respectfully remind the Examiner that the court in *Lilly* was concerned with the description of a claimed cDNA sequence. Because the particular cDNA had not been cloned before, the court required the sequence of the particular cDNA cor compliance with the written description requirement. Here, the claimed

invention is not a novel DNA sequence. It is a novel recombinant microorganism that functions as a therapeutic agent. Emphasis solely on structure, as if a novel DNA sequence were claimed, is misguided and results in application of an incorrect standard for determining compliance with the written description requirement.

An appropriate standard has been adopted by the Federal Circuit Court of Appeals and the USPTO Both agree that relevant identifying characteristics other than structure can be used to satisfy the written description requirement.

> In its Guidelines, the PTO has determined that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Guidelines, 66 Fed. Reg. at 1106 (emphasis added by court). *Enzo Biochem. Inc., v. Gen-Probe Inc.*, No 01-1230 (Fed. Cir. July 15, 2002).

Thus, the written description requirement can be met by a patent specification that describes a combination of functional and structural characteristics of a claimed invention. Here, Applicants have claimed microorganisms that express extracellular sugars or oligosaccharides that mimic receptors for pathogenic organisms. The function of the invention, (*e.g.*, blocking the binding of pathogenic organisms to oligosaccharide receptors) correlates with the structure of the claimed invention, (*e.g.*, a recombinant microorganism expressing an oligosaccharide that mimics the structure of an oligosaccharide receptor for a pathogenic organism). Because it is well-established that sugars or oligosaccharides that repeat the structure of an oligosaccharide receptor (*e.g.*, receptor mimics) will bind specifically to the same receptor ligands (*e.g.* a toxin), the function and structure of the invention correlate and the written description requirement is met.

The Office Action improperly rejected original claims as lacking adequate written description. According to the M.P.E.P., there is a strong presumption that an adequate written description of the claimed invention is present in the application as filed,

including the original claims. M.P.E.P. 2163 (I) (A). The Examiner must present evidence or reasoning to the contrary to rebut the presumption. M.P.E.P. 2163.04. The Examiner has not done so here.

The Examiner asserts that the written description requirement is not met because of alleged lack description of certain members of the claimed genus, including microorganisms with reduced production of external masking polysaccharides, microorganisms resistant to the major families of colicins, recombinant microorganisms with naturally occurring glycosyltransferases, and microorganisms where genes encoding the glycosyltransferase are modified to stabilize phase variations.

Applicants respectfully traverse and bring to the Examiner's attention description of those elements in the specification. Description of reduced production of external masking oligonucleotides is found for example at page 24, lines 5-10 of the specification. Description of microorganisms resistant to the major families of colicins is found for example at page 23, lines 15-18 of the specification. Description of recombinant microorganisms with naturally occurring glycosyltransferases is found for example at original claim 64. Description of microorganisms with genes encoding glycosyltransferase that have been modified to stabilize phase variations is found for example at page 42, lines 25-32 of the specification.

Applicants assert that the Examiner has not presented a reasonable basis to challenge the adequacy of the written description. The Examiner has the burden of presenting by a preponderance of the evidence why a person of skill in the art would not recognize in the disclosure a description of the invention defined by the claims. The Office Action presents no evidence that, based on the disclosure in the specification, one of skill would not recognize a microorganism with reduced production of external masking oligonucleotides, or microorganisms resistant to the major families of colicins, or recombinant microorganisms with naturally occurring glycosyltransferases, or microorganisms where genes encoding the glycosyltransferase are modified to stabilize phase variations. The specification and claims as filed provide adequate written description of the claimed invention.

The Examiner is also concerned that the inventors were not in possession of the claimed invention at the time of filing because not all species of the claimed genus were reduced to practice. However, the Examiner does acknowledge that the specification provides written description and enablement for a recombinant *E. coli* bacterium comprising an exogenous glycosyltransferase for production of a specific sugar moiety that mimics a bacterial toxin receptor. (Office Action at pages 7 and 10.) Applicants have added new claims 117-119 to this embodiment.

Under United States patent law, invention refers to the inventor's conception of an idea, rather than to a physical manifestation of the idea, *e.g.*, actual reduction to practice. The United States Supreme Court has stated that "[i]t is well settled that an invention may be patented before it is reduced to practice." *Pfaff v. Wells*, 119 S. Ct. 304, 309 (1998). The applicant can demonstrate conception and satisfy the requirement for written description by describing the invention with "sufficient clearness and precision" to allow one of skill in the art to practice the invention as intended by the inventor.

Here, Applicants have described the invention with sufficient clarity and precision to allow one of skill in the art to make and to use the claimed genus, thus satisfying the written description requirement. Applicants have provided examples of multiple sugars and oligosaccharides that can be used as receptor mimics (specification at pages 26-36); instructions for identifying appropriate acceptor molecules (specification at page 10, lines 19-24 and page 31,lines 5-15); and instructions for selecting an appropriate glycosyltransferase to conjugate the binding molecule to the acceptor molecule (specification at pages 10-18 and page 31, line 21 continuing through page32, line 10).

Using the methods described in the specification, Applicants also provide examples of how to practice the invention as intended by the inventor. In Examples 1 and 2, Applicants showed that the structures of Shiga toxins Stx1 and Stx2 can be mimicked using an *E. coli* LPS molecule modified by glycosyltransferases originally isolated from *Neisseria* species. Applicants showed that the Shiga toxin mimics could be constructed in a variety of *E. coli* strains and in a different bacterial species, *S.*

typhimurium. Using *in vitro* and *in vivo* assays, Applicants also showed that the *E. coli* cells expressing the receptor mimic were able to neutralize the Shiga toxins. In Example 3, Applicants disclose a mimic of a second Shiga toxin isolate, Stx2e, which has an additional N-galNAc moiety in the binding molecule. Applicants obtained both an appropriate glycosyltransferase gene and a gene encoding an accessory enzyme (*e.g.*, UDP-GalNAc-4-epimerase) to construct the receptor mimic in *E. coli*. Applicants showed that *E. coli* cells expressing the receptor mimic were able to neutralize the toxin *in vitro*. Example 4 discloses construction of a mimic of a receptor for a third toxin, a *C. difficile* toxin. Example 5 discloses construction of a mimic of a receptor for traveler's diarrhea and cholera toxin from a enterotoxigenic *E. coli* and *Vibrio cholerae*, respectively. Other examples, for binding toxins of uropathogenic *E. coli,* porcine enterotoxigenic *E. coli*, *Entamoeba histolycum*, and rotavirus are also disclosed.

The description of the invention and the many different examples provided by Applicants clearly demonstrate how Applicants intended the claimed invention to be practiced. Briefly, the user first identifies the structure of a toxin receptor of interest (*e.g.*, a recptor mimic). The user identifies an appropriate glycosyltransferase to synthesize the mimic in a recombinant organism. The user then tests the activity of the recombinant organism using *in vitro* and *in vivo* assays described and exemplified in the specification. Thus, the application provides precise and clear descriptions of the steps for the user to practice the invention in treating the pathogenic organisms of his or her choice.

In view of the above remarks, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, written description be withdrawn.

VIII. Claim Rejections Under 35 U.S.C. §112, First Paragraph, Enablement

Claims 1-9, 15, 25, 36-37, 41, 43, 45-70, 73-85, 88-91, 94, 97-107, and 110 are rejected under 35 U.S.C. §112, first paragraph for alleged lack of enablement. The Examiner alleges that the specification is not enabling for the full scope of the claimed invention because allegedly, practice of the invention requires undue

experimentation by one of skill in the art. To the extent the rejections apply to the amended claims, applicants respectfully traverse.

A. The specification contains sufficient written description to enable one of skill in the art to practice the claimed genus.

The Examiner alleges that, because of deficiencies in written description, one of skill in the art would not know how to make and use the claimed genus for its intended operation. Applicants respectfully traverse and assert that the claimed genus is both adequately described and enabled by the specification.

With respect to the written description requirement for a claimed genus, description of a representative number of species does not require such specificity that support is provided for each species embraced by the genus. (MPEP 2163 (II)(A)(3)(a)(ii)). Applicants have described sufficient species to provide description of the entire claimed genus. As described above, Applicants have provided numerous examples and description of receptor mimics that can be synthesized by the claimed recombinant microorganisms. Applicants have also provided description of multiple microorganisms that can be used in the claimed invention and provide examples for use of two different species of microorganisms, *E. coli* and *S. typhimurium*. (Examples 1 and 2.) Thus, Applicants have provided a representative number of species and have adequately described the claimed genus.

With respect to the enablement requirement for a claimed genus, representative examples and a statement applicable to the genus as a whole are sufficient for enablement is one of skill in the art can use the genus without undue experimentation. (MPEP 2164.02.) The Examiner must advance adequate reasons to establish why one of skill could not use the genus as a whole without undue experimentation. As described in more detail below, the specification provides many representative examples of the claimed genus and a statement that applies to the genus as a whole is found, for example, at page 8, lines 23-31. In addition, the Office Action has not established why one of skill could not use the genus as a whole without undue experimentation. Thus, Applicants

have provided adequate written description to enable one of skill to use the claimed genus without undo experimentation.

B. The full scope of the claimed invention is enabled by the specification.

For a variety of reasons, the Examiner alleges that the full scope of the claimed invention is not enabled because the specification allegedly fails to provide guidance for one of skill to make and use the invention. Applicants respectfully traverse the rejection.

Applicants assert that the Examiner has not met his burden to establish a reasonable basis to question the enablement provided for the claimed invention. Where a specification contains a teaching of the manner and process of making and using the invention as is the case here, the subject matter must by taken as being in compliance with the enablement requirement, unless there is reason to doubt the objective truth of statements containing enabling support. As explained fully below, the Examiner has not provided such a basis.

In addition, the Examiner alleges that undue experimentation is required for one of skill in the art to practice several aspects of the claimed invention. In some aspects, the Examiner appears to have misunderstood the elements comprising the claimed invention. In other aspects, the Examiner appears to have focused improperly on inoperative embodiments, leading to the conclusion that undue experimentation would be required to practice the methods of the claimed invention. However, the proper test of enablement is "whether one skilled in the art could make or use the claimed invention from the disclosure in the patent coupled with information known in the art without undue experimentation" (*see, e.g.*, MPEP §2164.01). Claims reading on inoperative embodiments are enabled if the skilled artisan understands how to avoid inoperative embodiments. (*See, In re Cook and Merigold*, 169 USPQ 299, 301 (C.C.P.A. 1971)). In the present application, one of skill would know how to avoid inoperative embodiments and make therapeutically active recombinant bacteria, without undue experimentation.

Moreover, the present application provides guidance in the form of assays and working examples for identification of therapeutically active recombinant bacteria.

For example, the Office Action alleges that the specification lacks guidance for one of skill in the art to attach a binding moiety, (*e.g.*, a sugar residue that mimics a pathogenic receptor) to an acceptor molecule. (Office Action at page 13.) The Office Action also alleges that LPS, an extracellular sugar molecule found in gram negative bacteria, is the only surface expressed acceptor molecule that is enabled by the specification.

Applicants respectfully disagree. The specification at page 10, lines 19-24 clearly identifies a large number of potential extracellular acceptor molecules, including glycolipids, glycoproteins, capsular polysaccharides of either gram-positive or gram-negative bacteria, teichoic acids and lipoteichoic acids of gram-positive bacteria or other carbohydrates that are anchored in the delivery microorganism.

The specification also teaches and claims methods to alter the composition of an acceptor molecule, *e.g.*, express a recombinant glycosyltransferase with the capability of adding a desired binding moiety to a sugar residue found in the acceptor molecule. The Examiner has provided no objective reason to believe that recombinant glycosyltransferases of the appropriate specificity will be unable to alter acceptor molecules other than the LPS molecule.

The Examiner alleges that sugar moieties based on glycoproteins or glycolipids are not enabled as receptor mimics for toxins, adhesins, and other ligands. The Examiner appear to believe that the entire glycolipid or glycoprotein is required for binding by the pathogenic organism, and thus must be recapitulated in the binding moiety of the receptor mimic. (Office Action at page 15.) Applicants respectfully point out that only the oligosaccharide moiety of the glycolipid or glycoprotein is used as a receptor mimic. Expression of an entire exogenous glycolipid or glycoprotein is not required. In addition, Applicants have provided examples of receptor mimics based on the oligosaccharide portions of glycolipids and glycoproteins. The receptor for Botulinum toxin is believed to be a sialic acid containing glycoprotein or glycolipid present on

neurons. (Specification at page 26, lines 22-24.) The exemplified Stx receptor mimic is based on a glycolipid receptor (Examples 1 and 2.) Similarly, *C. difficile* exotoxin A of Example 4 binds to human glycolipids.

The Examiner alleges that because of limited knowledge of plasmid replication in non-*E. coli* bacteria, expression of exogenous glycosyltransferases is enabled only in *E. coli* bacteria. Applicants respectfully bring to the Examiner's attention Example 1, where several strains of *E. coli* and *S. typhimurium* were transformed with appropriate *Neisseria* glycosyltransferase encoding genes and used to neutralize Shigella toxin in vitro. (Specification at page 47, Table 9, see also page 23 lines 30-31.) Applicants also point out that other microorganisms have been used to express exogenous proteins and genes for many years, for example, *Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*. Other bacterial genera, known as food bacteria, can be used, *e.g.*, *Acidophilus*, *Lactobacillus*, *Lactococcus*, or *Bifidobacterium*. (Specification at page 23 line 32 continuing through page 24, line 4; and original claims 58 and 83.)

In addition, Applicants point out that those of skill are aware of the requirements for a functional expression plasmid in a microorganism, *e.g.*, an origin of replication, a functional promoter and transcription system, and a functional translation start site. The Examiner cited a reference that appears to assert that the timing of replication is different in *B. subtilus* than in *E. coli*. Even with such differences, those of skill in the art will be able to recognize functional plasmids. Thus, those of skill will be able to determine whether a functional expression system is available for a given microorganism and will be able to avoid making inoperative embodiments of the claimed invention.

The Examiner alleges that expression of sugar moieties in *E. coli* cannot be extrapolated to expression of sugar moieties in eukaryotic microorganisms. The Examiner alleges differences in post-transcriptional processing between prokaryotes and eukaryotes will act as a barrier to use of the present invention. The of skill in the art are aware that proteins encoded by eukaryotic cDNAs are expressed in *E. coli*. For example bovine UDP-Gal α-1→ 3-galactosyltransferase is expressed in *E. coli*. Similarly, the

Examiner presents no evidence that bacterial genes or other genes lacking transcriptional processing signals (*e.g.*, cDNAs) cannot be expressed in eukaryotic cells. Applicants have provided assays to determine if glycosyltransferase genes are expressed. Inoperative embodiments can thus be determined without undue experimentation.

The Examiner alleges that that support is not provided for determining colicin resistant microorganisms other than *E. coli*. Applicants respectfully disagree. Those of skill in the art are aware of assays to determine the toxicity of a substance to a bacterial isolate. For example, it is a simple matter to make culture plates containing a toxin of interest (*e.g.*, a colicin), plate a bacterial strain of interest on the plates, and assay colony growth. Thus, assays for colicin sensitivity are within the expertise of those of skill in the art. In addition, if a given bacterial strain was found to be colicin sensitive, those of skill would know to either select a different bacterial strain or to modify the strain as taught in the specification at page 23, lines 16-18.

The Examiner alleges that support is not provided to identify and modify glycosyltransferases subject to phase variation. Applicants respectfully disagree. The specification has numerous examples of phase variation and its avoidance. At page 42, lines 29 to 32 phase variation is described as the presence of poly-G tracts within an open reading frame. The open reading frame is thus, susceptible to slipped strand mispairing and premature termination during replication, which results in premature termination of the open reading frame during translation of the encoded glycosyltransferase, *e.g.*, the protein is not expressed. The following examples describe recognition and modification of frame slipping within glycosyltransferase genes: *lgtC* at pages 43-44, *lgtD* at page 55, and *lgtAB* at page 60.

In addition, if a gene with phase slipping was not identified and corrected, the resulting recombinant glycosyltransferase would potentially be inactive. However, routine experimentation described in the application would uncover the defect in glycosyltransferase activity, allowing the user to select an operative embodiment of the recombinant enzyme for use in the invention.

The Examiner alleges that the specification fails to provide support for administration of the recombinant bacteria of the invention after infection with a pathogenic organism. Applicants respectfully disagree and draw the Examiner's attention to Example 2, pages 51 to 52, which shows that mice treated with a receptor mimic after STEC challenge had better survival rates and times than untreated mice.

The USPTO has also spoken on this issue in the Training Materials for Examining Applications With Respect to 35 U.S.C. §112, First Paragraph-Enablement-Chemical/Biotechnical Applications. " If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. Section 112, is satisfied." Training Materials at III.A.2.b.ii., citing *In re Johnson*, 282 F.2d 370, 373, 127 USPQ 216, 219 (CCPA 1960); and *In re Hitchings*, 342 F.2d 80, 87, 144 USPQ 637, 643 (CCPA 1965). Thus, "[i]t is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation." Training Materials at III.A.2.b.ii.

The Examiner alleges that support is provided only for making or using a mimic of a bacterial toxin. Applicants respectfully disagree. The use of non-bacterial toxins is enabled by the specification. Many examples of non-bacterial toxins are given, *e.g.*, including eukaryotic toxins from *Entamoeba histolyticum* (page 27), *Acanthamoeba* (page 29), *Candida albicans* (page 29), and *Aspergillus fumigatus*; and viral toxins from porcine *Rotovirus* (page 27), *Influenza* virus, *Paramyxovirus* (page 30), human and bovine *Coronavirus*, and *Parvovirus* (page 31). Oligosaccharides that can be used as non-bacterial toxin receptor mimics are also disclosed. Thus, the specification enables the use of mimics of receptors of a variety of microorganism associated toxins.

In view of the above remarks, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, enablement be withdrawn.

IX. Claim Rejections Under 35 U.S.C. §112, Second Paragraph, Indefiniteness

Claims 1, 36, 52-53, 60, 62-65, 73-75, 79-80, 97-107, and 110 are rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite. To the extent the rejection applies to the claims as amended, Applicants respectfully traverse.

Claims 1 and 36 are objected to as using improper Markush format. Applicants have inserted the word "and" before the last species in the Markush group of claim 36.

Claims 1, 52, 53, and 60 are rejected for alleged lack of antecedent basis of "the receptor mimic." Claims 52, 53, and 60 have been amended to recite "a mimic of a receptor for a toxin or adhesin of a pathogenic organism." Support for this amendment is found, for example in the specification at page 25, lines11-14. Claim 52 is rejected for allegedly lacking antecedent basis for "the exogenous transferases". Claim 52 has been amended to read "exogenous glycosyltransferases." Support for this amendment is found in original claim 1.

Claims 62, 79, and 101 are rejected for allegedly lacking antecedent basis for the term "the gut." Claim 62 is amended to read "the gut of the animal." Animal has antecedent basis in claim 1. Similarly, claim 101 is amended to read "the gut of the mammal." Mammal has antecedent basis in claim 88. Claim 79 is amended to replace "the gut" with "the gastrointestinal mucosal surface." Support and antecedent basis for this amendment is found in claim 78.

Claims 63, 80, and 102 are rejected for allegedly lacking antecedent basis for the term "the major families of colicins." Claims 63, 80, and 102 are amended to read "a colicin from a major family of colicins" rather than "the major families of colicins." Support for this amendment is found in the specification at, for example, page 23, lines 15-18.

Claim 64 is rejected for use of the allegedly indefinite phrase "wherein all of some of the one or more glycosyl transferases are naturally occurring." Claim 64 is amended to read "wherein at least one of the glycosyltransferases is naturally occurring." Support for this amendment is found in original claim 64. This amendment apprises

those of skill in the art of the scope of the invention. Similarly, claims 65 and 75 are rejected for use of the allegedly indefinite phrase "wherein all of some of the one or more glycosyl transferases." Claims 65 and 75 are amended to read "wherein at least one of the glycosyltransferases is modified to reduce phase variation." Support for this amendment is found in the specification at, for example, page 18, lines 10-12.

Claims 89-90, 97-107, and 110 are rejected as allegedly being indefinite for reciting "a receptor." As suggested by the Examiner, Applicants have amended claims 89-90, 97-107, and 110 to recite "the receptor."

Claims 84 and 106 are rejected for allegedly omitting the relationship between elements of the claims. Claim 84 is amended to recite that the delivery microorganism is killed "before administration of the pharmaceutical preparation." Claim 106 is amended to recite that the delivery microorganism is killed "before administration to the mammal." Support for these amendments is found in the specification at, for example page 22, lines 17-24.

In view of the above amendments and remarks, Applicants respectfully request that the rejection under 35 U.S.C. §112, second paragraph be withdrawn.

X. Claim Rejections Under 35 U.S.C. §102(a) and §103(a)

Claims 1-8, 25, 46, 51, 53, 55-59, 63, 66-69, 74, 76, 78-80, 82-85, 88-90, 97-99, 102, and 104-107 are rejected under 35 U.S.C. §102(a) as allegedly anticipated by Paton *et al.*, *Nature Med.* 6:265-270 (2000). Claims 1-9, 15, 25, 37, 41, 43, 46, 51-52, 55-59, 63, 66-70, 73-74, 76, 78, 80, 82-85, 88-91, 94, 98-99, 102, and 104-107 are rejected under 35 U.S.C. §103(a) as allegedly obvious in view of the same reference, *e.g.*, Paton *et al.*, *Nature Med.* 6:265-270 (2000).

Applicants respectfully traverse both rejections. Paton *et al.* became publicly available after the earliest effective priority date of the application and therefore, is not properly cited as prior art. Applicants continue to assert that the earliest effective filing date for the application is the date of filing of a priority document, the Australian Provisional Application No. PQ2757. The Australian Provisional Application was filed

on September 10, 1999, well before the March 2000 publication date of Paton *et al.* At the request of the Examiner, Applicants provide with this response a certified copy of the Australian priority document for filing with the USPTO.

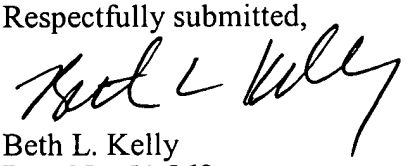
In view of the above amendments and remarks, Applicants respectfully request that the rejection under 35 U.S.C. §§102(a) and 103(a) be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, The Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,



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APPENDIX A
VERSION WITH MARKINGS TO SHOW CHANGES MADE TO THE ABSTRACT

Chimeric carbohydrates produced by recombinant microorganism carrying exogenous [glycosyl transferases] glycosyltransferases act with or without exogenous enzymes required for synthesis or nucleotide synthesis precursors. These recombinant microorganism can be used [as a means] for competitively inhibiting the binding of toxins or adhesins to receptors of mucosal surfaces, especially gastrointestinal surface. In particular chimeric sugar moieties have been made for lipopolysaccharides, in recombinant microorganism that present multiple copies of the oligosaccharides. The oligosaccharide moieties so presented act as receptor mimic for toxins and adhesins. A number have been [synthesise] synthesized and have been shown to confer protection against attack by pathogenic organisms or their products *in vitro* and [an] *in vivo* .

APPENDIX B
VERSION WITH MARKINGS TO SHOW CHANGES MADE TO THE CLAIMS

36. (Once amended) The recombinant microorganism of claim 1, wherein the animal is selected from humans, pigs, cows, horses, canines, felines, chickens, turkeys, goats, rabbits, sheep, geese, and ducks.

52. (Once amended) The recombinant microorganism as in claim 1, wherein a combination of sugars of the acceptor molecule and the one or more sugars transferred to the acceptor molecule by the exogenous glycosyltransferases make up the entirety of [the receptor mimic] a mimic of a receptor for a toxin or adhesin of a pathogenic organism.

53. (Once amended) The recombinant microorganism as in claim 1, wherein the completed acceptor molecule has a terminal residue to which the exogenous glycosyltransferases transfer sugars to make up [the receptor mimic] a mimic of a receptor for a toxin or adhesin of a pathogenic organism.

58. (Once amended) The recombinant microorganism as in claim 56, wherein said microorganism is selected from a genus selected from the group consisting of *Escherichia, Salmonella, Acidophilus, Lactobacillus, Lactococcus*, and *Bifidobacterium*.

60. (Once amended) The recombinant microorganism as in claim 1, wherein the microorganism is chosen by reason of having reduced production of external masking polysaccharide molecules other than said acceptor molecule to enhance exposure of [the receptor mimic] a mimic of a receptor for a toxin or adhesin of a pathogenic organism.

61. (Once amended) The recombinant microorganism as in claim 60, wherein the microorganism has reduced production of external molecules selected from the group comprising a slime layer, capsule, or exopolysaccharide.

62. (Once amended) The recombinant microorganism as in claim 1, wherein the microorganism is selected to provide some resistance to antimicrobial activity of microflora potentially resident in the gut of the animal.

63. (Once amended) The recombinant microorganism as in claim 1, wherein the microorganism is resistant to a colicin from a major [families] family of colicins.

64. (Once amended) The recombinant microorganism as in claim 1, wherein [all or some of the] at least one [or more glycosyl transferases are] glycosyltransferase is naturally occurring.

65. (Once amended) The recombinant microorganism as in claim 1, wherein genes encoding [all or some of the] at least one [or more glycosyl transferases are] glycosyltransferase is modified to [stabilise] stabilize phase variation.

66. (Once amended) A recombinant microorganism expressing one or more exogenous sugar transferases, or one or more exogenous nucleotide sugar precursor [synthesising] synthesizing enzymes, said microorganism also expressing an acceptor molecule, said one or more exogenous sugar transferases being specific for the transfer of one or more sugar residues represented progressively from a non reducing terminal end of a receptor of either a toxin or an adhesin of a pathogenic organism, the exogenous sugar transferases progressively transferring said one or more sugar resides onto the acceptor molecule to thereby form a chimeric carbohydrate molecule with an exposed

receptor mimic, said sugar precursor enzymes forming nucleotide precursors that are transferred to said acceptor molecule to make up said chimeric carbohydrate, said exposed receptor mimic capable of binding the toxin or the adhesin.

67. (Once amended) A pharmaceutical preparation for administration to a mucosal surface, said preparation [including] comprising a delivery microorganism or a partially or fully purified non-toxic preparation of a carbohydrate molecule therefrom, at least a part of said carbohydrate molecule acting as an exposed receptor mimic, said receptor mimic capable of binding a toxin or an adhesin of a pathogen that normally binds to said mucosal surface, said pharmaceutical preparation being carried in a pharmaceutically acceptable excipient.

74. (Once amended) The pharmaceutical preparation as in claim 67, wherein one or more exogenous nucleotide sugar precursor [synthesising] synthesizing enzymes are also expressed by said delivery [organism] microorganism, said sugar precursor enzymes forming precursors to make up said chimeric carbohydrate.

75. (Once amended) The pharmaceutical preparation as in claim 67, wherein genes encoding [the all or some of the] at least one [or more glycosyl transferases are] glycosyltransferase is modified to prevent phase variation.

79. (Once amended) The pharmaceutical preparation as in claim 78, wherein the delivery microorganism is selected to provide some resistance to antimicrobial activity of microflora potentially resident in the [gut] gastrointestinal mucosal surface.

80. (Once amended) The pharmaceutical preparation as in claim 79, wherein the delivery microorganism is resistant to a colicin from a major [families] family of colicins.

83. (Once amended) The pharmaceutical preparation as in claim 82, wherein the delivery microorganism belongs to an enteric genera selected from the group consisting of *Escherichia, Salmonella, Acidophilus, Lactobacillus, Lactococcus, Streptococcus*, and *Bifidobacterium*.

84. (Once amended) The pharmaceutical preparation as in claim 67, wherein the delivery microorganism is killed before administration of the pharmaceutical preparation.

89. (Once amended) The method of administering [a] the receptor mimic as in claim 88, wherein the delivery microorganism is a recombinant microorganism expressing one or more exogenous sugar transferases and an acceptor molecule, said one or more exogenous sugar transferases being specific for transfer of one or more sugar residues represented progressively from a non reducing terminal end of a receptor of either a toxin or an adhesin of a pathogenic organism, the exogenous sugar transferases progressively transferring said one or more sugar resides onto the acceptor molecule to thereby form a chimeric carbohydrate molecule with the exposed receptor mimic being exposed, said exposed receptor mimic capable of binding the toxin or the adhesin.

90. (Once amended) The method of administering [a] the receptor mimic as in claim 88, wherein the receptor mimic is a mimic of the receptor of a toxin.

97. (Once amended) The method of administering [a] the receptor mimic as in claim 88, wherein one or more exogenous nucleotide sugar precursor [synthesising]

synthesizing enzymes are also expressed by said delivery [organism] microorganism, said sugar precursor enzymes forming precursors to make up said chimeric carbohydrate.

98. (Once amended) The method of administering [a] the receptor mimic as in claim 88, wherein the delivery microorganism is non harmful and live.

99. (Once amended) The method of administering [a] the receptor mimic as in claim 88, wherein the administration is enterally.

100. (Once amended) The method of administering [a] the receptor mimic as in claim 99, wherein the delivery microorganism is protected by a protective capsule or held within a protective matrix.

101. (Once amended) The method of administering [a] the receptor mimic as in claim 99, wherein the delivery microorganism is selected to provide some resistance to antimicrobial activity of microflora potentially resident in the gut of the mammal.

102. (Once amended) The method of administering [a] the receptor mimic as in claim 99, wherein the delivery microorganism is resistant to a colicin from a major [families] family of colicins.

103. (Once amended) The method of administering [a] the receptor mimic as in claim 99, wherein the delivery microorganism is grown under conditions to induce acid tolerance.

104. (Once amended) The method of administering [a] the receptor mimic as in claim 99, wherein the delivery microorganism is enteric.

105. (Once amended) The method of administering [a] the receptor mimic as in claim 104, wherein the delivery microorganism is belongs to an enteric genera selected from the group consisting of Escherichia, Salmonella, Acidophilus, Lactobacillus, Lactococcus, and Bifidobacterium.

106. (Once amended) The method of administering [a] the receptor mimic as in claim 88, wherein the delivery microorganism is killed before administration to the mammal.

107. (Once amended) The method of administering [a] the receptor mimic as in claim 106, wherein the delivery microorganism is killed by treatment with a chemical agent selected from the group consisting of formalin[,] or thiomersal, or a bactericidal antibiotic, or by exposure to heat or to UV irradiation.

110. (Once amended) The method of administering [a] the receptor mimic as in claim 88, wherein the receptor mimic is that of a porcine rotavirus or shiga like toxin active in pigs, [including] comprising the step of adding the delivery microorganism to pig feed or drink.

117. (New) A recombinant *E. coli* that displays on its surface a binding moiety that, when administered to an animal, competes with a ligand for binding to a receptor for the ligand, wherein the binding moiety comprises an oligosaccharide which comprises a sugar residue that is attached to an acceptor moiety by a glycosyltransferase that is encoded by an exogenous nucleic acid which is present in the microorganism.

118. (New) The recombinant *E. coli* of claim 117, wherein the oligosaccharide is Galα[1→4]Galβ[1→4]Glc.

119. (New) The recombinant *E. coli* of claim 117, wherein the oligosaccharide is GalNAcβ[1→3]Galα[1→4]Galβ[1→4]Glc.

APPENDIX C
PENDING AND AMENDED CLAIMS

1. (As filed) A recombinant microorganism that displays on its surface a binding moiety that, when administered to an animal, competes with a ligand for binding to a receptor for the ligand, wherein the binding moiety comprises an oligosaccharide which comprises a sugar residue that is attached to an acceptor moiety by a glycosyltransferase that is encoded by an exogenous nucleic acid which is present in the microorganism.

2. (As filed) The recombinant microorganism of claim 1, wherein the microorganism is selected from the group consisting of bacteria, fungi, Mycoplasma, and yeast.

3. (As filed) The recombinant microorganism of claim 1, wherein the oligosaccharide further comprises at least a second sugar residue that is attached to an acceptor moiety by at least a second glycosyltransferase.

4. (As filed) The recombinant microorganism of claim 3, wherein the second glycosyltransferase is encoded by a second exogenous nucleic acid which is present in the microorganism.

5. (As filed) The recombinant microorganism of claim 1, wherein the receptor is present on a surface of a cell.

6. (As filed) The recombinant microorganism of claim 5, wherein the cell is an epithelial or endothelial cell that comprises a mucosal membrane of an animal.

7. (As filed) The recombinant microorganism of claim 1, wherein the binding moiety is a mimic of a receptor for a toxin or adhesin of a pathogenic organism.

8. (As filed) The recombinant microorganism of claim 7, wherein the toxin is an enterotoxin.

9. (As filed) The recombinant microorganism of claim 7, wherein the toxin is selected from the group consisting of shiga toxins, clostridial toxins, cholera toxins, *E. coli* enterotoxins, and Staphylococcal enterotoxins.

15. (As filed) The recombinant microorganism of claim 9, wherein the toxin is selected from the group consisting of cholera toxin, *E. coli* heat labile enterotoxin types I and II, and ST toxins.

25. (As filed) The recombinant microorganism of claim 1, wherein the binding moiety competes with a pathogenic organism for binding to a corresponding receptor on an animal epithelial or endothelial cell.

36. (Once amended) The recombinant microorganism of claim 1, wherein the animal is selected from humans, pigs, cows, horses, canines, felines, chickens, turkeys, goats, rabbits, sheep, geese, and ducks.

37. (As filed) The recombinant microorganism of claim 1, wherein the binding moiety comprises an oligosaccharide selected from the group consisting of:

Galα[1→4]Galβ[1→4]Glc,

Galα[1→4]Galβ,

GalNAcβ[1→3]Galα[1→4]Galβ[1→4]Glc,

Galβ[1→4]GlcNAc,

Galα[1→3]Galβ[1→4]Glc,

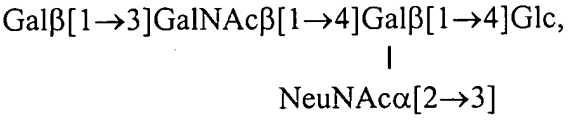
Galα[1→3]Galβ[1→4]GlcNAc,

Galβ[1→4]GlcNAcβ[1→3]Galβ[1→4]Glc,

Glcα[1→6]Glc,

Glcα[1→6]Glcα[1→6]Glc,

NeuNAc,



Galβ[1→3]GalNAcβ[1→4]Galβ[1→4]Glc,
NeuNAcα[2→3]

Galβ[1→3]GalNAcβ[1→4]Galβ[1→4]Glc,

GalNAcβ[1→4]Gal,

GalNAc,

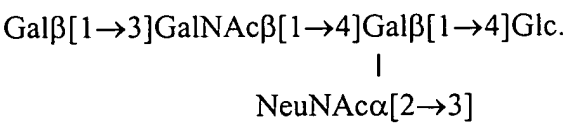
Gal,

NeuGc→GM_3, and

NeuNAc→GM_3.

41. (As filed) The recombinant microorganism of claim 37, wherein the binding moiety comprises NeuNAc.

43. (As filed) The recombinant microorganism of claim 37, wherein the binding moiety comprises the oligosaccharide:



Galβ[1→3]GalNAcβ[1→4]Galβ[1→4]Glc.
NeuNAcα[2→3]

45. (As filed) The recombinant microorganism of claim 1, wherein the binding moiety is a mimic of natural receptor for adhesins or toxins produced by a micro-organism selected from a group of genera consisting of *Escherichia, Salmonella, Shigella, Citrobacter, Helicobacter, Yersinia, Vibrio, Aeromonas, Campylobacter, Pseudomonas, Pasteurella, Neisseria, Haemophilus, Klebsiella, Staphylococcus, Streptococcus, Clostridium*, rotavirus, and *Entamoeba*.

46. (As filed) The recombinant microorganism of claim 1, wherein the microorganism further comprises one or more exogenous enzymes involved in synthesis of a nucleotide sugar which serves as a donor for the glycosyltransferase.

47. (As filed) The recombinant microorganism of claim 46, wherein the nucleotide sugar is selected from the group consisting of GDP-Man, UDP-Glc, UDP-Gal, UDP-GlcNAc, UDP-GalNAc, CMP-sialic acid, GDP-Fuc, and UDP-xylose.

48. (As filed) The recombinant microorganism of claim 46, wherein the enzyme is a nucleotide sugar synthetase.

49. (As filed) The recombinant microorganism of claim 46, wherein the enzyme is involved in synthesis of a nucleotide that comprises the nucleotide sugar.

50. (As filed) The recombinant microorganism of claim 46, wherein the enzyme is involved in synthesis of a sugar that comprises the nucleotide sugar.

51. (As filed) The recombinant microorganism of claim 46, wherein the one or more sugars transferred to the acceptor molecule by the exogenous glycosyltransferases make up the entirety of the receptor mimic.

52. (Once amended) The recombinant microorganism as in claim 1, wherein a combination of sugars of the acceptor molecule and the one or more sugars transferred to the acceptor molecule by the exogenous glycosyltransferases make up the entirety of a mimic of a receptor for a toxin or adhesin of a pathogenic organism.

53. (Once amended) The recombinant microorganism as in claim 1, wherein the completed acceptor molecule has a terminal residue to which the exogenous glycosyltransferases transfer sugars to make up a mimic of a receptor for a toxin or adhesin of a pathogenic organism.

54. (As filed) The recombinant microorganism as in claim 1, wherein the acceptor molecule is an incomplete endogenous molecule and at least one of the exogenous glycosyltransferases competes with an endogenous glycosyltransferase to transfer said sugar molecule thereto.

55. (As filed) The recombinant microorganism as in claim 1, wherein the binding moiety is anchored to the outer surface of the microorganism.

56. (As filed) The recombinant microorganism as in claim 56, wherein the microorganism is gram negative and the acceptor molecule is a lipopolysaccharide.

57. (As filed) The recombinant microorganism as in claim 55, wherein the acceptor molecule is all or a portion of the core of the lipopolysaccharide.

58. (Once amended) The recombinant microorganism as in claim 56, wherein said microorganism is selected from a genus selected from the group consisting of *Escherichia, Salmonella, Acidophilus, Lactobacillus, Lactococcus*, and *Bifidobacterium*.

59. (As filed) The recombinant microorganism as in claim 58, wherein said microorganism is selected from a species selected from the group consisting of *Escherichia coli* and *Salmonella enterica* sv typhimurium.

60. (Once amended) The recombinant microorganism as in claim 1, wherein the microorganism is chosen by reason of having reduced production of external masking polysaccharide molecules other than said acceptor molecule to enhance exposure of a mimic of a receptor for a toxin or adhesin of a pathogenic organism.

61. (Once amended) The recombinant microorganism as in claim 60, wherein the microorganism has reduced production of external molecules selected from the group comprising a slime layer, capsule, or exopolysaccharide.

62. (Once amended) The recombinant microorganism as in claim 1, wherein the microorganism is selected to provide some resistance to antimicrobial activity of microflora potentially resident in the gut of the animal.

63. (Once amended) The recombinant microorganism as in claim 1, wherein the microorganism is resistant to a colicin from a major family of colicins.

64. (Once amended) The recombinant microorganism as in claim 1, wherein at least one glycosyltransferase is naturally occurring.

65. (Once amended) The recombinant microorganism as in claim 1, wherein genes encoding at least one glycosyltransferase is modified to stabilize phase variation.

66. (Once amended) A recombinant microorganism expressing one or more exogenous sugar transferases, or one or more exogenous nucleotide sugar precursor synthesizing enzymes, said microorganism also expressing an acceptor molecule, said one or more exogenous sugar transferases being specific for the transfer of one or more sugar residues represented progressively from a non reducing terminal end of a receptor of either a toxin or an adhesin of a pathogenic organism, the exogenous sugar transferases progressively transferring said one or more sugar resides onto the acceptor molecule to thereby form a chimeric carbohydrate molecule with an exposed receptor mimic, said sugar precursor enzymes forming nucleotide precursors that are transferred to said acceptor molecule to make up said chimeric carbohydrate, said exposed receptor mimic capable of binding the toxin or the adhesin.

67. (Once amended) A pharmaceutical preparation for administration to a mucosal surface, said preparation comprising a delivery microorganism or a partially or fully purified non-toxic preparation of a carbohydrate molecule therefrom, at least a part of said carbohydrate molecule acting as an exposed receptor mimic, said receptor mimic capable of binding a toxin or an adhesin of a pathogen that normally binds to said

mucosal surface, said pharmaceutical preparation being carried in a pharmaceutically acceptable excipient.

68. (As filed) The pharmaceutical preparation as in claim 67, wherein the delivery microorganism is a recombinant microorganism expressing one or more exogenous sugar transferases and an acceptor molecule, said one or more exogenous sugar transferases being specific for transfer of one or more sugar residues represented progressively from a non reducing terminal end of a receptor of either a toxin or an adhesin of a pathogenic organism, said delivery microorganism expressing an acceptor molecule, and progressively transferring said one or more sugar resides onto the acceptor molecule to thereby form the chimeric carbohydrate molecule with the receptor mimic, said exposed receptor mimic capable of binding the toxin or the adhesin.

69. (As filed) The pharmaceutical preparation as in claim 67, wherein the receptor mimic is a mimic of the receptor of a toxin.

70. (As filed) The pharmaceutical preparation as in claim 69, wherein the toxin is selected from the group consisting of shiga toxins, clostridial toxins, cholera toxins, *E. coli* enterotoxins, and Staphylococcal enterotoxins.

73. (As filed) The pharmaceutical preparation as in claim 67, wherein the receptor mimic is partially or wholly formed within a sugar moiety of selected from the group comprising:

Galα[1→4]Galβ[1→4]Glc,

Galα[1→4]Galβ,

GalNAcβ[1→3]Galα[1→4]Galβ[1→4]Glc,

Galβ[1→4]GlcNAc,

Galα[1→3]Galβ[1→4]Glc,

Galα[1→3]Galβ[1→4]GlcNAc,

Galβ[1→4]GlcNAcβ[1→3]Galβ[1→4]Glc,

Glcα[1→6]Glc,

Glcα[1→6]Glcα[1→6]Glc,

NeuNAc,

Galβ[1→3]GalNAcβ[1→4]Galβ[1→4]Glc,
|
NeuNAcα[2→3]

Galβ[1→3]GalNAcβ[1→4]Galβ[1→4]Glc,

GalNAcβ[1→4]Gal,

GalNAc,

Gal,

NeuGc→GM_3, and

NeuNAc→GM_3.

74. (Once amended) The pharmaceutical preparation as in claim 67, wherein one or more exogenous nucleotide sugar precursor synthesizing enzymes are also expressed by said delivery microorganism, said sugar precursor enzymes forming precursors to make up said chimeric carbohydrate.

75. (Once amended) The pharmaceutical preparation as in claim 67, wherein genes encoding at least one glycosyltransferase is modified to prevent phase variation.

76. (As filed) The pharmaceutical preparation as in claim 67, wherein the delivery microorganism is non harmful and live.

77. (As filed) The pharmaceutical preparation as in claim 67, wherein the delivery microorganism is protected by a protective capsule or held within a protective matrix.

78. (As filed) The pharmaceutical preparation as in claim 67, wherein the target mucosal surface is gastrointestinal.

79. (Once amended) The pharmaceutical preparation as in claim 78, wherein the delivery microorganism is selected to provide some resistance to antimicrobial activity of microflora potentially resident in the gastrointestinal mucosal surface.

80. (Once amended) The pharmaceutical preparation as in claim 79, wherein the delivery microorganism is resistant to a colicin from a major family of colicins.

81. (As filed) The pharmaceutical preparation as in claim 79, wherein the delivery microorganism is grown under conditions to induce acid tolerance.

82. (As filed) The pharmaceutical preparation as in claim 78, wherein the delivery microorganism is enteric.

83. (Once amended) The pharmaceutical preparation as in claim 82, wherein the delivery microorganism belongs to an enteric genera selected from the group consisting of *Escherichia, Salmonella, Acidophilus, Lactobacillus, Lactococcus, Streptococcus*, and *Bifidobacterium*.

84. (Once amended) The pharmaceutical preparation as in claim 67, wherein the delivery microorganism is killed before administration of the pharmaceutical preparation.

85. (As filed) The pharmaceutical preparation as in claim 84, wherein the delivery microorganism is killed by treatment with a chemical agent selected from the group consisting of formalin or thiomersal, or by treatment with a bactericidal antibiotic, or by exposure to heat or UV irradiation.

88. (As filed) A method of administering a receptor mimic to a mucosal surface of a mammal, the method comprising the administration of a quantity of a delivery microorganism, or parts thereof, the delivery microorganism exhibiting one or more sugars in a configuration to form an exposed receptor mimic, the receptor mimic being a mimic of a receptor of a pathogen, said quantity being sufficient to reduce adherence of the pathogen or a toxin produced by the pathogen to the mucosal surface.

89. (Once amended) The method of administering the receptor mimic as in claim 88, wherein the delivery microorganism is a recombinant microorganism expressing one or more exogenous sugar transferases and an acceptor molecule, said one or more exogenous sugar transferases being specific for transfer of one or more sugar residues represented progressively from a non reducing terminal end of a receptor of either a toxin or an adhesin of a pathogenic organism, the exogenous sugar transferases progressively transferring said one or more sugar resides onto the acceptor molecule to thereby form a chimeric carbohydrate molecule with the exposed receptor mimic being exposed, said exposed receptor mimic capable of binding the toxin or the adhesin.

90. (Once amended) The method of administering the receptor mimic as in claim 88, wherein the receptor mimic is a mimic of the receptor of a toxin.

91. (As filed) The method of administering a receptor mimic as in claim 90, wherein the toxin is selected from the group consisting of shiga toxins, clostridial toxins, cholera toxins, *E. coli* enterotoxins, and staphylococcal enterotoxins.

94. (As filed) The method of administering a receptor mimic as in claim 88, wherein the receptor mimic is partially or wholly formed within a sugar moiety of selected from the group comprising:

Galα[1$\rightarrow$4]Galβ[1$\rightarrow$4]Glc,

Galα[1→4]Galβ,

GalNAcβ[1→3]Galα[1→4]Galβ[1→4]Glc,

Galβ[1→4]GlcNAc,

Galα[1→3]Galβ[1→4]Glc,

Galα[1→3]Galβ[1→4]GlcNAc,

Galβ[1→4]GlcNAcβ[1→3]Galβ[1→4]Glc,

Glcα[1→6]Glc,

Glcα[1→6]Glcα[1→6]Glc,

NeuNAc,

Galβ[1→3]GalNAcβ[1→4]Galβ[1→4]Glc,
|
NeuNAcα[2→3]

Galβ[1→3]GalNAcβ[1→4]Galβ[1→4]Glc,

GalNAcβ[1→4]Gal,

GalNAc,

Gal,

NeuGc→GM_3, and

NeuNAc→GM_3.

97. (Once amended) The method of administering the receptor mimic as in claim 88, wherein one or more exogenous nucleotide sugar precursor synthesizing enzymes are also expressed by said delivery microorganism, said sugar precursor enzymes forming precursors to make up said chimeric carbohydrate.

98. (Once amended) The method of administering the receptor mimic as in claim 88, wherein the delivery microorganism is non harmful and live.

99. (Once amended) The method of administering the receptor mimic as in claim 88, wherein the administration is enterally.

100. (Once amended) The method of administering the receptor mimic as in claim 99, wherein the delivery microorganism is protected by a protective capsule or held within a protective matrix.

101. (Once amended) The method of administering the receptor mimic as in claim 99, wherein the delivery microorganism is selected to provide some resistance to antimicrobial activity of microflora potentially resident in the gut of the mammal.

102. (Once amended) The method of administering the receptor mimic as in claim 99, wherein the delivery microorganism is resistant to a colicin from a major family of colicins.

103. (Once amended) The method of administering the receptor mimic as in claim 99, wherein the delivery microorganism is grown under conditions to induce acid tolerance.

104. (Once amended) The method of administering the receptor mimic as in claim 99, wherein the delivery microorganism is enteric.

105. (Once amended) The method of administering the receptor mimic as in claim 104, wherein the delivery microorganism is belongs to an enteric genera selected from the group consisting of Escherichia, Salmonella, Acidophilus, Lactobacillus, Lactococcus, and Bifidobacterium.

106. (Once amended) The method of administering the receptor mimic as in claim 88, wherein the delivery microorganism is killed before administration to the mammal.

107. (Once amended) The method of administering the receptor mimic as in claim 106, wherein the delivery microorganism is killed by treatment with a chemical agent selected from the group consisting of formalin or thiomersal, or a bactericidal antibiotic, or by exposure to heat or to UV irradiation.

110. (Once amended) The method of administering the receptor mimic as in claim 88, wherein the receptor mimic is that of a porcine rotavirus or shiga like toxin active in pigs, comprising the step of adding the delivery microorganism to pig feed or drink.

117. (New) A recombinant *E. coli* that displays on its surface a binding moiety that, when administered to an animal, competes with a ligand for binding to a receptor for the ligand, wherein the binding moiety comprises an oligosaccharide which comprises a sugar residue that is attached to an acceptor moiety by a glycosyltransferase that is encoded by an exogenous nucleic acid which is present in the microorganism.

118. (New) The recombinant *E. coli* of claim 117, wherein the oligosaccharide is Galα[1→4]Galβ[1→4]Glc.

119. (New) The recombinant *E. coli* of claim 117, wherein the oligosaccharide is GalNAcβ[1→3]Galα[1→4]Galβ[1→4]Glc.